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Delivery of the growth restricted preterm fetus

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Stillbirth, neonatal death, and neurodevelopmental abnormalities are significantly more common in growth restricted fetuses than in those with normal growth.¹ Health care for women with pregnancies complicated by preterm fetal growth restriction needs complex assessment and planning, including the ability to differentiate the constitutionally small fetus from the pathologically small fetus; determine the cause of small fetal size; manage common maternal comorbidities; and decide when to deliver a growth restricted fetus to maximise chances for survival and minimise maternal risk.

Fetal growth restriction is defined differently by various organisations and authors. In a survey of Irish obstetricians and trainees, more than 30 different definitions of fetal growth restriction were identified.² Fetal size below the tenth percentile, a common definition, can be the result of familial traits (ie, the constitutionally small fetus), intrinsic fetal abnormalities (eg, fetal alcohol syndrome or aneuploidy), or uteroplacental abnormalities.³ For individuals with uteroplacental abnormalities, the timing of delivery based on ongoing assessment of maternal and fetal wellbeing is crucial.

The dominant theory is that, at some point, the fetal side of an abnormal placenta will be so resistant to perfusion that the fetus will adapt, increasing right-sided heart pressures,^{4,5} which will result in increased flow pulsatility in the ductus venosus (DV), ultimately to the point that loss of the A wave during pulsed Doppler interrogation of the DV occurs. The fetus might retain normal oxygenation to a point, as shown by normal fetal heart rate tracing, but ultimately becomes acidotic and hypoxic. At what point along this pathway should the fetus be delivered to decrease the risk of brain injury and death?

In *The Lancet*, Christoph Lees and colleagues⁶ report the results of the Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) to address this question. Fetal growth restriction was defined as a fetal abdominal circumference lower than the tenth percentile and abnormal umbilical artery Doppler with a pulsatility index of more than the 95th percentile, with or without reversed or absent end-diastolic flow. With these inclusion criteria, the study group is enriched with participants with placental disease as the likely cause of fetal growth restriction. In TRUFFLE,⁶ 503 women were randomly assigned to one of three groups for timing of delivery: abnormal variability on cardiotocography based on computerised interpretation (166 women), DV resistance index greater than the 95th percentile (DV p95; 167 women), and DV with no A wave (DV no A; 170 women). Safety net criteria were described by which delivery was indicated irrespective of randomised group. The primary

outcome was survival without neurodevelopmental impairment at 2 years. Comprehensive standardised neurodevelopmental assessments at 2 years, corrected for prematurity, were done by trained psychologists or paediatricians masked to study group.

TRUFFLE is one of few studies to examine long-term outcomes in growth restricted fetuses. The growth restriction intervention trial (GRIT)⁷ randomly assigned patients to early or delayed delivery when evidence of fetal compromise was present, but the obstetrician was in equipoise regarding whether delivery was indicated. Neonatal outcomes, childhood morbidity at 2 years, and morbidity at school age did not differ between groups in GRIT, which did not help clinicians with regard to timing of delivery in growth restricted fetuses.

The proportions of infants in TRUFFLE who survived without neurodevelopmental impairment in those randomly assigned to delivery in the cardiotocography short-term variation (CTG STV; 111 [77%] infants of 144 with known outcome, 95% CI 70–83), DV p95 (119 [84%] infants of 142, 77–89), and DV no A (133 [85%] infants of 157, 78–90) groups did not differ ($p=0.09$). However, in survivors, neurodevelopmental impairment was least impaired in those randomly assigned to the DV no A group (133 [95%] of 140; 95% CI 90–98) as compared with those in the CTG STV delivery group (111 [85%] of 131, 95% CI 78–90; $p=0.005$), which was at the cost of a non-significant change in perinatal and infant mortality.

The results of TRUFFLE support the notion that fetal venous Doppler abnormalities precede fetal acidosis and hypoxia in most growth restricted preterm fetuses.⁶ However, the overall outcomes of the study participants were much better than predicted, even in the group delivered for standard cardiotocography indications. Pregnancies in the TRUFFLE study were monitored at least once per week, but the study does not mention how many were monitored more frequently. To address these outcomes, what frequency of monitoring is appropriate? Once a fetus starts to make adaptations, how quickly do the adaptations maintain normal oxygenation and pH deteriorate? The average latency after enrolment was 8 days, but at least one delivery occurred at 40 weeks and 4 days.

What sort of fetal or neonatal assessments were done for intrinsic fetal defects in TRUFFLE, through imaging techniques, autopsy, karyotype, CMV testing, and microarray analysis is not known. Were those who died or survived with neurodevelopment impairment different in potentially detectable ways from those who survived with no such impairment? What prenatal diagnostic testing is ideal? Computerised cardiotocography interpretation is uncommon worldwide. How generalisable are the results if so-called interpretation by eye is used? Would achievement of these good outcomes need a switch to computerised cardiotocography interpretation?

82% of growth restricted neonates survived without neurodevelopmental impairment at 2 years in TRUFFLE, which is encouraging. Translation of these results from research to the clinical setting will require that accurate DV flow measurements have widespread availability, and that testing intervals are short enough to identify the fetus before injury occurs. The challenge for the obstetric community now is to consider how to duplicate these results in their own settings. Lees and colleagues⁶ have shown that relying on DV A wave

changes and computerised interpretation of cardiotocography data, in addition to safety net criteria, improves survival and neurodevelopmental outcomes in the growth restricted fetus with poor placental function. The bar has been raised: are we prepared to reach it?

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